a first compartment contains an amount of a freeze-dried material which upon addition of water for injection is capable of reconstituting a unit dosage of a bioresorbable injectable implant suitable for administration to a human patient in need thereof; and

wherein a second compartment contains a unit doasage of said water for injection.

REMARKS

Status of Claims:

Claims 21-36 were pending in the application. New claims 37-52 are hereby added. Claims 21-52 are now pending in the application. Each of the pending claims defines an invention that is novel and unobvious over the cited art. Favorable consideration of this case is respectfully requested.

Newly Presented Claims 37-53:

New claim 37 recites subject matter presented in claim 21 and additional subject matter relating to inclusion of a surfactant (disclosed at page 5, lines 3-5) and the resorbability of the gel (disclosed at page 4, lines 21-24).

New claims 38-40 specify the gelling agent supporting disclosure for which was presented at page 4, lines 26-37.

New claim 41 specifies the surfactant supporting disclosure for which was presented at page 5, lines 1-5.

New claims 42 and 43 relate to freeze-drying and apyrogenic mannitol as a cryoprotective reagent (disclosed at page 5, line 36 to page 6, line 11).

New claims 44-46 relate to a method of making the inventive implant, disclosure for which was provided at page 5, lines 17-35.

New claims 47-49 relate to dosage and packaging forms of the inventive implant; disclosure for which was presented at page 5, lines 7-13.

New claim 50 relates to a method of making a freeze-dried composition capable of reconstituting the inventive implant; disclosure of which was provided at page 6, lines 5-24.

New claims 51 and 52 relate to single-dosage kit forms of the inventive implant; disclosure of which was provided at page 5, lines 7-13.

Other Claim Amendments:

Claim 24 is hereby amended to recite the mean diameter of the microparticles or microspheres is less than 150 micrometers. Support for this recitation is present at page 3, lines 5-9.

Claim Objections:

Claim 21 was objected to for awkward grammer. Solely for purposes of clarity, the recitation "microparticles in suspension in gel" is hereby amended to recite "microparticles suspended in a gel."

Claims 28 and 29 were objected to for reciting "Dalton." Claims 28 and 29 are hereby amended, for purposes of clarity only, to recite the plural "Daltons."

Rejections Under 35 U.S.C. § 112, 2nd Paragraph:

Claims 27 and 34-36 were rejected under 35 U.S.C. § 112, 2nd Paragraph, as being indefinite.

Claim 27 was rejected for improperly reciting Markush language. Claim 27 is hereby amended per the Examiner's suggestion to properly recite the Markush formulaic merely for purposes of format and not to restrict or otherwise affect the scope of the claims.

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Claims 34 and 35 were rejected because the basis for the concentration was deemed to be unclear. Claims 34 and 35 are hereby amended to clarify the basis for the recitation of concentration. Support for this amendment was present in the original disclosure at, for example, page 4, lines 26-31.

Claim 36 was rejected as reciting a comma that rendered the claim indefinite. Claim 36 is hereby amended, for purposes of clarity only, to delete said comma per the Examiner's suggestion.

Summary of the Present Invention:

The present invention relates to an implant for subcutaneous or intradermal injection, intended for human administration. The present invention relates to an implant for subcutaneous or intradermal injection, intended fro use in humans in reparative or restorative plastic surgery. The inventive implant is also useful in esthetic dermatology for filling wrinkles, fine lines, skin cracks, and scars due to acne and other causes. The inventive implant is also useful in dentistry for filling gums. An aspect of the present invention is the provision of an implant that does not require test of allergenicity by virtue of its being free of materials of animal origin (see page 5, lines 14-16). The inventive implant contains of microparticles or microspheres suspended in a gel. Each component of the inventive implant is selected to be free of materials of animal origin. Furthermore, the inventive implant is designed to be hydrolyzed and absorbed by the human body over the course of a controllable and predictable time.

An aspect of the present invention is controlled bioresorption. In view of the implant as a foreign body, a non-resorbable implant is to be specifically avoided. (Page 2, line 38 - page 3, line 1).

An aspect of the present invention is the absence of allergenicity which is realized by at least two means. First, man-made materials known to produce adverse reactions , such as teflon pastes, are excluded. (Page 1, lines 19-25). Second, materials of animal origin are excluded. (Page 5, lines 14-16).

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An aspect of the present invention is its ready syringability. (Page 3, lines 2-9). The present invention realizes syringeability by the means of suspending the microspheres or microparticles in a gel.

Rejection Under 35 U.S.C. § 102(e):

Claims 21, 24, 27-31, and 34-36 were rejected under 35 U.S.C. § 102(e) as being anticipated by Ron (5.597.897).). Ron does not anticipate any of claims 21, 24, 27-31, or 34-36. In determining anticipation, no claim limitation may be ignored. See *Pac-Tex, Inc. v. Amerace Corp.*, 14 USPQ2d 1871 (Fed. Cir. 1990). Anticipation requires the disclosure, in a prior art reference, of each and every recitation as set forth in the claims. See *Titanium Metals Corp. v. Banner*, 227 USPQ 773 (Fed. Cir 1985), *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081 (Fed. Cir 1986), and *Akzo N.V. v. U.S. International Trade Commissioner*, 1 USPQ2d 1241 (Fed. Cir 1986). There must be no difference between the claimed invention and reference disclosure for an anticipation rejection under 35 U.S.C. § 102. See *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001 (CAFC 1991) and *Studiengesellschaft Kohle GmbH v. Dart Industries*, 220 USPQ 841 (CAFC 1984). The evidentiary record fails to teach each recitation of the cited claims.

The Examiner cites Ron as disclosing a sequestering agent and osteogenic protein together forming the gel. This conclusion in the Office Action is without foundation and is incorrect. First, Ron is silent as to a gel as a vehicle. Although Ron does employ CMC, one of the gelling agents of the present invention, Ron nowhere discloses using CMC to form a gel. Rather, Ron employs CMC and other materials to form a "malleable (putty-like) composition." (Column 4, line 66). Ron does not recite CMC as a gelling agent, rather Ron recites CMC as an osteogenic protein-sequestering material. "The osteogenic protein-sequestering material useful in the practice of the subject invention is a pharmaceutically acceptable material having a viscosity and polarity such that, when added to an

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osteogenic protein/porous particle combination, a malleable(putty-like) composite is formed that handles appropriately for surgical implantation." (Column 4, lines 62-67). CMC is cited as the most preferred sequestering agent. "A preferred family of sequestering agents is cellulosic materials such as alkylcellulose...the most preferred being the cationic salts of carboxymethylcellulose (CMC). (Column 5, lines 13-19).

An aspect of the present invention as discussed in the specification, is the complete absence of materials of animal origin. (See page 5, lines 14-16). Claim 21 is hereby amended to emphasize fact that the exclusion of materials of animal origin extends to, and includes, both the gel and the microparticulate components of the present invention. The present amendment does not narrow or further limit the claims. The Amendment filed February 1, 2002, specifically discussed Ron in view of the exclusion of materials of animal origin from the present invention. Claims 22-36 depend from claim 21 and therefore incorporate the exclusion of materials of animal origin.

In contradistinction to the present invention which excludes proteins and other materials of animal origin, Ron designs porous particulate materials specifically to serve as vehicles for proteins. "The polymer matrix component useful in the practice of the subject invention is a polymeric material that can be formed into porous particles ...thereby providing in-situ scaffolding for the osteogenic protein. (Column 3, lines 37-40). The invention of Ron is a combination of porous polymer particles a CMC sequestering agent as a combined vehicle to carry osteogenic proteins.

Rejection Under 35 U.S.C. § 103(a):

Claims 22, 23, 25, 26, 32 and 33 were rejected under 35 U.S.C. § 103(a) as being unpatentable solely over Ron.

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To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka.* All words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson.* (MPEP § 2143.03). When evaluating the scope of a claim, every limitation in the claim must be considered. See e.g. *In re Ochiai.* (MPEP § 2144.08). The evidentiary record fails to teach each limitation of the present invention.

Ron is disqualified because Ron relates to osteogenic proteins, i.e., materials of animal origin. To exclude the osteogenic proteins from Ron would be contrary to the suggestions and objectives of Ron. With regard to claims 22-23, 25-26, and 32-33 none of the concentration range of the particles, the diameter of the particles, the degradation time of the particles, nor the residual solvent is relevant to the exclusion of materials of animal origin. Further, as discussed above, Ron is silent as to formation of a gel vehicle.

With respect to claim 25, the Examiner acknowledges that the particle diameter of Ron is outside the range of the present invention. In support of his position, the Examiner advances only a conclusory statement to the effect that the diameter is a mere design choice and alleges that the applicants have not disclosed any advantage of their disclosed range. To the contrary, the applicants disclosed two advantages; first, to facilitate injection through a fine syringe, and second, to avoid creation of a palpable granular mass. (Page 3, lines 5-9). Moreover the particle diameter of Ron cannot be reduced to meet the claimed range of the present invention because to do so would defeat the purposes of Ron. Ron requires a particle diameter of 150 to 850 microns in order to create sufficient spacing between the particles to allow mammalian osteoprogenitor cells to infiltrate. (Column 3, lines 63-66). Where the Examiner proposes a combination that makes a prior art reference inoperable for its intended purpose, the resulting inoperable prior art reference is considered to teach away from the proposed combination, thereby supporting a showing of nonobviousness. *In re Gordon*, 733

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F.2d 900, 902 (Fed. Cir. 1984) (Finding no suggestion to modify a prior art device where the modification would make the device inoperable for its intended purpose).

Claims 21-25 and 30-31 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Scopelianos (EP 07 11794) in view of Orly (WO 93/13755). The Examiner argues that Scopelianos meets the claim language except for failing to disclose a gelation material for the liquid portion. Scopelianos and Orly each fails to meet the limitations of the present invention with respect to the composition of the microparticles. Scopelianos relates to ε-caprolactones and other monomers excluded from the present invention.

Orly relates to collagen-based compositions and to other materials of animal origin including atelocollagen and polysaccharides particularly including glycosaminoglycan. Materials of animal origin are specifically excluded by the present invention. Orly discusses an injectable composition based on the collagen, comprising microcapsules of atelcollagen or a mixture of atelcollagen and a polysaccharide. Heterologous collagen, i.e. bovine collagen, is suggested as the most efficient material in terms of biocompatibility and *in vivo* stability.

Collagen is not recited in the list of polymers in claim 1. In fact, it is mentioned in the present specification that one is trying to remedy the drawbacks of known products such as collagen, which exhibit a very fast resorption, allergy problems and problems linked to using products of animal origin. For instance, see page 1, lines 26-31 and page 2, lines 20-21 of the specification. The cited abstract to Orly is silent as to gels. Orly recites microcapsules and a viscous solution. Neither Scopelianos nor Orly recite a gel. Scopelianos does not relate to gels, rather, Scopelianos relates to a liquid carrier comprising a liquid polymer (page 3, line 8) said liquid suspending particulate material (page 3, line15).

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The mere fact that cited art may be modified in the manner suggested by the Examiner does not make this modification obvious, unless the cited art suggest the desirability of the modification. No such suggestion appears in the cited art in this matter. The Examiner's attention is kindly directed to *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002); *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999). Since both Scopelianos and Orly are silent as to gels, there can be no suggestion in the art itself for forming a gel.

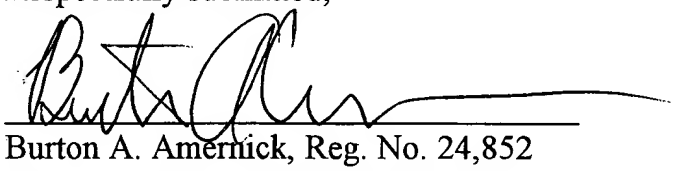
Conclusion:

Accordingly, it is respectfully requested that the foregoing amendments be entered, that the application as so amended receive an examination on the merits, and that the claims as now presented receive an early allowance.

In the event the Examiner believes an interview might serve to advance the prosecution of this application in any way, the undersigned attorney is available at the telephone number noted below.

The Commissioner is hereby authorized to charge any fees or credit any overpayment associated with this communication, including any extension fees or fees for the net addition of claims, to Deposit Account No. 22-0185.

Respectfully submitted,



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APPENDIX
(Amended Claims)

21. (Twice amended) A bioresorbable injectable implant for human administration consisting essentially of:

bioresorbable microspheres or microparticles [in suspension in gel] suspended in a gel consisting essentially of materials of non-animal origin,

said microspheres or microparticles consisting of at least one polymer of non-animal origin [chosen] selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers.

24. (Amended) The injectable implant for human administration, according to claim 21, wherein said microspheres or microparticles have a mean diameter of from 5 to less than 150 micrometers.

27. (Amended) The injectable implant for human administration[,] according to claim 21, wherein said microspheres or microparticles consists of a polymer selected from the group consisting of [the group] poly-L-lactic acid, poly-D-lactic acid and mixtures thereof.

28. (Amended) The injectable implant for human administration, according to claim 21, wherein said [polylactic acid] polymer has a molecular mass of between 70,000 and 175,000 [Dalton] Daltons.

29. (Amended) The injectable implant for human administration, according to claim 21, wherein said [polylactic acid] polymer has a molecular mass of between 120,000 and 170,000[Dalton] Daltons.

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34. (Amended) The injectable implant for human administration, according to claim 21, wherein said gel [comprises a gelling agent consisting] consists essentially of water and 0.1 to 7.5% by weight carboxymethylcellulose (CMC) or hydroxypropylmethylcellulose (HPMC) [at a concentration by weight of 0.1 to 7.5%].

35. (Amended) The injectable implant for human administration, according to claim 21, wherein said gel [comprises a gelling agent consisting] consists essentially of water and 0.1 to 5.0% by weight carboxymethylcellulose (CMC) or hydroxypropylmethylcellulose (HPMC) [at a concentration by weight of 0.1 to 5.0%].

36. (Amended) The product obtained by freeze-drying the injectable implant for human administration[,] according to claim 21, wherein said product is capable of reconstituting an injectable implant for human administration upon addition of water for injection.

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